



Prospective Associations of Serum Tumor Necrosis Factor-Alpha and Employment on Suicidal Behaviors Over 1 Year in Depressive Patients Receiving Psychopharmacotherapy

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Objective This study explored both the individual and combined effects of serum tumor necrosis factor-alpha (sTNF- α) levels and employment status on suicidal behavior (SB) in patients with depressive disorders undergoing pharmacologic treatment.

Methods Baseline measurements of sTNF- α levels were taken, and employment status was determined. Over a 1-year period of stepwise pharmacotherapy, SB was monitored and categorized into increased suicidal severity and fatal/non-fatal suicide attempts. Logistic regression models adjusted for relevant covariates were used to analyze the individual and interactive associations between sTNF- α levels, employment status, and these two forms of SB.

Results Unemployment was significantly associated with both forms of SB, whereas sTNF- α levels alone did not show a significant correlation. However, lower sTNF- α levels combined with employment were associated with the lowest incidence rates of both SB categories, demonstrating significant interactive effects after adjustment.

Conclusion The study demonstrates that the prospective associations of sTNF- α levels for SB is enhanced when combined with employment status in patients receiving pharmacological treatment for depressive disorders. These findings suggest that integrating biological markers with socio-economic factors can improve the assessment and management of suicide risk. **Psychiatry Investig 2025;22(7):748-756**

Keywords Tumor necrosis factor-alpha; Employment; Suicidal behavior; Depression; Psychopharmacotherapy.

INTRODUCTION

Suicide emerges as one of the most severe public health challenges in modern society. Nearly 800,000 individuals lose their lives to suicide each year, and these figures suggest that the incidence of suicidal thoughts and attempts far outpaces documented suicidal deaths.¹ The identification of risk factors is crucial for monitoring and preventing suicidal behaviors (SB), yet this task is often complicated by the reliance on subjective reports, which can obscure the true risk factors due to their variable accuracy and reliability.² Given the distinct

pathophysiology associated with SB, which diverges significantly from other psychiatric conditions, there is a compelling need for objective biological measures that could enhance the predictability and preventiveness of suicide risk assessments.^{3,4}

Emerging scientific investigations have explored immune and inflammatory biomarkers as potential predictors of SB,⁵ drawing upon their established neurobiological connections to the hypothalamic-pituitary-adrenal axis and serotonin systems—key neurological mechanisms underlying mood modulation and stress response.⁶ Among these biomarkers, tumor necrosis factor-alpha (TNF- α), a pro-inflammatory cytokine involved in systemic inflammation and neuroinflammation has emerged as a noteworthy candidate. TNF- α is hypothesized to influence neural circuits and behavior patterns related to suicide.⁷ However, investigations into TNF- α as a standalone predictor of SB have shown inconsistent outcomes,⁸⁻¹⁰ and a meta-analysis did not establish a definitive connection between baseline TNF- α levels and SB.⁵

Furthermore, TNF- α levels are known to be affected by phys-

Received: February 5, 2025 Revised: March 27, 2025

Accepted: April 24, 2025

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ical activity,¹¹ which can serve as an indirect marker of such lifestyle factors through employment status¹²—a variable also correlated with various mental health outcomes, including SB.^{13,14} The interplay between biological markers and psychosocial factors suggests a complex interaction that can modulate SB risks. Employment, typically reflecting social engagement and economic stability, may interact with biological pathways influenced by TNF- α , thereby impacting the incidence and severity of SB in ways that remain incompletely elucidated.⁷

In South Korea, the suicide mortality rate stood at 24.1 per 100,000 people in 2020, the highest among Organization for Economic Cooperation and Development countries.¹⁵ With such a pronounced prevalence, particularly in individuals with depressive disorders—a condition strongly linked to SB—it becomes imperative to explore these interactions more deeply.¹⁶ Utilizing data from a prospective study of Korean patients diagnosed with depressive disorders, who were receiving stepwise psychopharmacological treatment strategies, this study aims to dissect the individual and combined associations of serum TNF- α levels and employment status on SB. We hypothesize that lower serum TNF- α levels, when combined with stable employment, are associated with reduced incidence of SB in patients undergoing treatment for depressive disorders. Conversely, higher TNF- α levels or unstable employment status may correlate with an increased risk of SB, highlighting the potential moderating role of socioeconomic factors in the biological pathways influencing suicide risk.

METHODS

Study framework

This research was conducted as part of the MAKE Biomarker discovery for Enhancing Antidepressant Treatment Effect and Response (MAKE BETTER) initiative. The foundational design and objectives of this study have been previously outlined.¹⁷ Comprehensive socio-demographic, clinical baseline characteristics, and treatment-related data during the acute (assessments at 3, 6, 9, and 12 weeks) and continuation phases (assessments at 6, 9, and 12 months) of treatment were meticulously collected. This information was gathered using a meticulously designed clinical report form, which was administered by research coordinators. These coordinators were systematically blinded to the specific treatment approaches assigned to study participants. The study protocol received ethical approval from the Institutional Review Board of Chonnam National University Hospital (CNUH 2012-014), ensuring strict adherence to ethical standards in clinical research.

Participants

Individuals diagnosed with depressive disorders were sys-

tematically enrolled from the outpatient psychiatric services at CNUH over a period extending from March 2012 to April 2017. This enrollment approach represents a form of convenience nonprobability sampling, where all patients visiting the department during this timeframe and meeting the eligibility criteria were assessed and included upon their consent. This method was chosen due to practical accessibility and the specificity of the study setting, allowing us to examine a comprehensive group of patients initiating a new course of antidepressant therapy, applicable to both initial and recurrent depressive episodes. Comprehensive criteria for participant eligibility are detailed in a Supplementary Material. To maintain the focus and clarity of the investigation on pharmacological interventions within the MAKE BETTER program, patients receiving additional forms of therapy such as psychotherapy or repetitive Transcranial Magnetic Stimulation during the study period were excluded. Informed consent was rigorously sought, with all participants receiving and signing consent forms prior to inclusion in the study.

Baseline exposures

Serum TNF- α

Before collecting blood samples, participants were required to abstain from eating—though water intake was allowed—from the previous evening. Upon arriving for their appointment, they were asked to rest calmly for a period ranging from 25 to 45 minutes to stabilize their physiological state. Blood samples (10 mL) were collected into dry tubes and immediately stored in a refrigerator at 2°C to 4°C for 3 to 6 hours. Centrifugation was performed at 3000×g for 15 minutes at 4°C on the day of blood sampling. Subsequently, the serum samples were immediately frozen and stored at -80°C in the clinical laboratories of CNUH. Samples were thawed only just before the assays, after being stored for 2 to 7 years. The concentrations of serum TNF- α (sTNF- α) were then measured using the Human TNF- α Quantikine HS ELISA Kit (HSTA00D, R&D Systems) at the Global Clinical Central Lab located in Yongin, Korea. Data on the intra- and inter-assay coefficients of variation of sTNF- α were reported as 2.03% and 6.53%, respectively, across 20 test runs. For the purposes of analysis, the levels of sTNF- α were divided into low and high categories, which were determined based on the median value of the cohort.

Employment status

In this study, employment status was categorized based on the presence or absence of annual income. Participants reporting a consistent annual income through salary or business ownership were categorized as “employed,” while those with-

out documented income streams, including homemakers and individuals without formal economic participation, were classified as “unemployed.” This dichotomous classification is consistent with methodologies employed in various socioeconomic studies, which often distinguish employment status to assess economic activity and its psychosocial impacts.¹⁸

Baseline covariates

The study captured a range of socio-demographic variables, including age, sex, years of education, marital status (categorized as currently married or not), and living arrangements (whether living alone or with others). Clinically, participants were diagnosed with depressive disorders, either major depressive disorder or other forms, with additional specifiers such as melancholic or atypical features noted. Further clinical details included age at first onset, illness duration, the number of past depressive episodes, duration of the current episode, family history of depression, and the presence of concurrent physical disorders, assessed via a comprehensive questionnaire covering 15 distinct systems or disorders. Smoking habits were also recorded, identifying individuals as current smokers or non-smokers. To evaluate depressive and anxiety symptoms, the Hospital Anxiety and Depression Scale (HADS) was utilized, with separate subscales for depression (HADS-D) and anxiety (HADS-A).¹⁹ Additionally, the Alcohol Use Disorders Identification Test was employed to screen for alcohol-related issues.²⁰ In all scales, higher scores were indicative of more severe symptoms.

Pharmacotherapy

Treatment protocols and initial assessments, including clinical symptoms, severity, physical comorbidities, medication history, and previous treatments, have been detailed in prior publications.^{17,21} Antidepressants such as bupropion, desvenlafaxine, and others were prescribed following established guidelines.^{22,23} Treatment adjustments during the acute (every 3 weeks) and continuation (every 3 months) phases were made based on effectiveness, tolerability, and patient preferences, considering options like switching, augmentation, or combination therapies using a variety of antidepressants and augmented drugs like lithium and atypical antipsychotics. Following the initial phase of antidepressant monotherapy, treatment steps were incremented each time an adjustment was made. These adjustments defined the progression through the treatment steps, typically involving up to four distinct phases (steps 1 through 4) based on the complexity and intensity of the pharmacological strategy. Progression beyond step 4 was rare, reflecting the structured approach to escalating care only as clinically necessary. This staged treatment model allowed for a systematic analysis of pharmacological impacts across dif-

ferent levels of treatment intensification.

Outcomes on SB

Increased suicidal severity

The severity of suicidal ideation was assessed using the suicidality item of the Brief Psychiatric Rating Scale.²⁴ This item measures thoughts of self-harm or death on a scale from 1 (not present) to 7 (extremely severe). It was evaluated at baseline and subsequently during every follow-up visit. An increase in severity from baseline during the study period indicated increased suicidal severity.

Fatal/non-fatal suicide attempt

A suicide attempt was defined as any act of deliberate self-harm with some degree of intent to die,²⁵ assessed throughout the pharmacotherapy period. Ambivalent intent was included, but acts without intent to die were not considered suicide attempts. Fatal outcomes, including death by suicide, were also recorded during the study period.

Statistical analysis

Baseline socio-demographic and clinical characteristics, as well as treatment steps throughout the year of pharmacotherapy, were analyzed based on employment status using either independent t-tests or the Mann-Whitney U test, based on normal distribution assessments by the Kolmogorov-Smirnov test, or χ^2 tests, depending on the nature of the data. Similar comparative analyses were conducted between groups with lower versus higher levels of sTNF- α , and among groups categorized by the presence of increased suicidal severity. Variables that showed statistical significance ($p < 0.05$) and were not highly collinear were chosen as covariates for subsequent analyses. The relationships between sTNF- α groups and employment status with the two identified types of SB were initially explored through logistic regression models. These relationships were subsequently examined with selected covariate adjustments. Furthermore, the combined interactive associations of sTNF- α levels and employment status on SB types were explored using multinomial logistic regression, with appropriate covariate controls. All statistical procedures were bidirectional and maintained a critical significance threshold of 0.05. The statistical analyses were executed using the SPSS software, version 27.0 (IBM Corp.).

RESULTS

Recruitment and participant flow

The recruitment and participant flow are detailed in Figure 1. Of the 1,262 initial participants, 1,094 (86.7%) contributed

blood samples for sTNF- α level analysis. Within the sampled group, 884 participants (80.8%) completed both the 12-week acute treatment phase and at least one follow-up session during the 6 to 12-month continuation phase, ultimately comprising the study's analytical cohort. Baseline comparisons revealed no significant demographic or clinical divergences between blood sample providers and non-providers. However, attrition at the 12-month mark was notably higher among participants who were unemployed or had melancholic features at baseline.

Participants characteristics relative to exposures and outcomes

Of the participants, 242 (27.4%) were identified as unemployed. The median (interquartile range) and mean $\pm$ standard deviation sTNF- α levels were recorded at 0.593 $\pm$ 0.4 pg/mL and 0.716 $\pm$ 0.5 pg/mL, respectively. Over the course of the 1-year pharmacotherapy, 155 participants (17.5%) experienced an increase in suicidal severity, and there were 38 cases (4.3%) of fatal/non-fatal suicide attempts, including 32 non-fatal and 6 fatal attempts. Characteristics stratified by employment status are detailed in Table 1, where unemployment was significantly linked to being male, unmarried, living alone, experiencing a higher number of depressive episodes, and elevated scores on the HADS-D. Unemployment was not significantly associated with sTNF- α levels. The differences in characteristics between participants with sTNF- α levels below versus above the median value are detailed in Supplementary Table 1. Notably, higher sTNF- α levels were significantly related to older age, male sex, lower educational attainment, older age at onset of depression, longer current episode duration, a greater number of physical disorders, and current smoking status. The relationships between characteristics and increased suicidal severity are analyzed in Supplementary Table 2. Noteworthy associations included male sex, not living alone, current smoking, higher HADS-D scores, and un-

dergoing more intensive treatment steps within the year. Based on these associations and the assessment of variable collinearity, the following covariates were selected for further adjusted analyses: age, sex, marital status, living situation, episode duration, physical disorder count, smoking status, HADS-D scores, and treatment step.

Individual associations of sTNF- α groups and employment status on SB

Table 2 provides specific relationships of sTNF- α groups and employment status with increased suicidal severity and the incidence of fatal/non-fatal suicide attempts throughout the 1-year pharmacotherapy. Initial findings indicated that higher sTNF- α levels were significantly associated with increased suicidal severity; however, this correlation lost statistical significance after covariate adjustments. In contrast, unemployment status demonstrated a consistent and significant correlation with both elevated suicidal severity and the incidence of fatal and non-fatal suicide attempts, maintaining its statistical significance before and after covariate adjustments.

Interactive associations of sTNF- α groups and employment status on SB

Figure 2 illustrates the combined interactive associations of sTNF- α groups and employment status on the outcomes related to SB. The incidence of both types of SBs was lowest among participants who had lower sTNF- α levels and were employed. In contrast, higher sTNF- α levels were significantly associated with an increase in both suicidal severity and fatal/non-fatal suicide attempts among those who were employed, with this association showing a statistically significant interaction after adjustment, an effect not observed among unemployed participants.

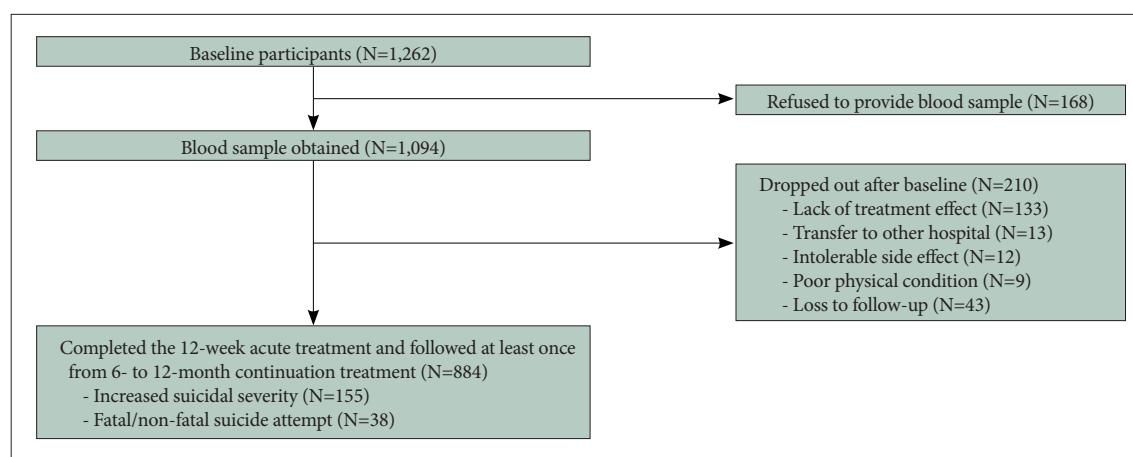


Figure 1. Participants recruitment process.

Table 1. Baseline characteristics compared by employment status (N=884)

	Employed (N=642)	Unemployed (N=242)	Statistical coefficients [†]	p-value
Socio-demographic characteristics				
Age (yr)	56.4 $\pm$ 13.9	58.6 $\pm$ 16.7	t=-1.879	0.061
Sex, female	457 (71.2)	150 (62.0)	χ^2 =6.914	0.009*
Education (yr)	9.0 (6.0)	9.0 (6.0)	U=75011.5	0.421
Marital status, unmarried	159 (24.8)	98 (40.5)	χ^2 =21.088	<0.001*
Living alone	80 (12.5)	51 (21.1)	χ^2 =10.329	0.001*
Clinical characteristics				
Major depressive disorder	547 (85.2)	214 (88.4)	χ^2 =1.528	0.216
Melancholic feature	102 (15.9)	39 (16.1)	χ^2 =0.007	0.934
Atypical feature	38 (5.9)	17 (7.0)	χ^2 =0.368	0.544
Age at onset (yr)	52.0 (22.0)	55.0 (29.0)	U=81159.0	0.079
Duration of illness (yr)	2.2 (9.0)	2.0 (9.0)	U=76861.0	0.808
Number of depressive episodes	1.0 (2.0)	1.5 (2.0)	U=85055.0	0.027*
Duration of present episode (month)	4.3 (7.0)	4.0 (7.0)	U=76686.0	0.768
Family history of depression	96 (15.0)	29 (12.0)	χ^2 =1.277	0.259
Number of physical disorders	1.0 (1.0)	2.0 (1.0)	U=81600.0	0.175
Current smoker	68 (10.6)	28 (11.6)	χ^2 =0.174	0.677
Serum tumor necrosis factor-alpha level (pg/mL)	0.6 (0.4)	0.6 (0.4)	U=76259.5	0.865
Assessment scales, scores				
Hospital Anxiety & Depression Scale				
Depression subscale	13.4 $\pm$ 4.0	14.4 $\pm$ 3.7	t=-3.471	0.001*
Anxiety subscale	11.7 $\pm$ 4.0	12.1 $\pm$ 4.0	t=-1.485	0.138
Alcohol Use Disorders Identification Test	1.0 (0.0)	1.0 (0.0)	U=74171.5	0.154
Treatment step over 1 year				
Step 1	245 (38.2)	81 (33.5)	χ^2 =3.194	0.363
Step 2	201 (31.3)	85 (35.1)		
Step 3	128 (19.9)	44 (18.2)		
Step 4	68 (10.6)	32 (13.2)		

Data are presented as mean $\pm$ standard deviation, median (interquartile range), or number (%) as appropriate. *p<0.05; [†]independent two sample t-test, Mann-Whitney U test, or χ^2 tests, as appropriate

DISCUSSION

In our investigation of individuals with depressive disorders undergoing stepwise pharmacotherapy, we observed that unemployment, rather than sTNF- α levels, had a significant association with the incidence of SB over the course of a 1-year follow-up. However, when considering the interactive effects, the combination of lower sTNF- α levels and employment correlated with the lowest incidence rates of both types of SB examined. Notably, these interactive effects demonstrated significant multiplicative interactions, remaining robust even after adjustments for pertinent covariates.

In our study, the individual associations between sTNF- α and SB, initially observed, did not remain significant after adjusting for relevant covariates. This outcome contrasts with

previous research that reported significant direct links between TNF- α levels and SB. Notably, earlier studies primarily focused on historical or current severity of suicidal ideation.^{8,26} Unlike these studies, our investigation uniquely contributes by examining the prospective relationship between TNF- α levels and SB over an extended period, marking a rare approach in this field. This divergence in findings may be attributed to differences in study design, population characteristics, or methods of assessing SB. Previous studies often investigated immediate contexts, such as existing suicidal thoughts or past attempts, and did not necessarily consider the prospective impact of TNF- α levels over time.⁸⁻¹⁰ The lack of significant findings after covariate adjustment in our study suggests that the relationship between TNF- α and SB might be influenced by more complex interactions than previously understood.

Table 2. Individual associations of sTNF- α levels and employment status with suicidal behavior during 1 year follow-up (N=884)

Exposure	Group	Increased suicidal severity†				Fatal/non-fatal suicide attempt			
		N (%)		OR (95% CI)		N (%)		OR (95% CI)	
		presence		Unadjusted	Adjusted‡	presence		Unadjusted	Adjusted‡
sTNF- α	Lower (N=434)	64 (14.7)		1.00	1.00	16 (3.7)		1.00	1.00
	Higher (N=450)	91 (20.2)		1.47 (1.03-2.08)*	1.39 (0.96-2.00)	22 (4.9)		1.34 (0.70-2.59)	1.17 (0.58-2.35)
Employment status	Employed (N=642)	98 (15.3)		1.00	1.00	20 (3.1)		1.00	1.00
	Unemployed (N=242)	57 (23.6)		1.71 (1.19-2.47)**	1.56 (1.06-2.30)*	18 (7.4)		2.50 (1.30-4.81)**	2.21 (1.09-4.49)*

* $p < 0.05$; ** $p < 0.01$; †increase in Brief Psychiatric Rating Scale suicidality item score during the follow-up compared to the baseline; ‡adjusted for age, sex, marital status, living alone, duration of present episode, number of physical disorders, current smoking, Hospital Anxiety & Depression Scale-depression subscale scores, and treatment step. sTNF- α , serum tumor necrosis factor- α ; OR, odds ratio; CI, confidence interval

This complexity indicates a need for further prospective studies to explore these dynamics more thoroughly and to draw more definitive conclusions on the biological and socio-economic factors influencing SB. Conversely, the significant association between unemployment status and SB observed in our study aligns with the majority of existing research, which consistently reports significant findings in this regard.^{13,14} This concordance supports the robustness and reliability of our results, underscoring the significant impact of socioeconomic factors on mental health outcomes in individuals with depressive disorders.

The significant predictive value of TNF- α for SB in employed participants, and particularly the markedly lower incidence of SB in the group characterized by both low TNF- α levels and employment, may be elucidated by considering both biological and psychosocial mechanisms. TNF- α , a pro-inflammatory cytokine, is known to influence brain function through its effects on neuroinflammation, neurotransmitter metabolism, and neural plasticity. Elevated levels of TNF- α have been associated with depressive symptoms,²⁷ which in turn are linked to increased suicidality.²⁸ In employed individuals, regular engagement in work might mitigate these biological impacts by promoting better mental health through structured routines, social connections, and a sense of purpose, all of which are protective factors against severe depression and suicidality.²⁹ Furthermore, employment may interact with physiological processes by providing psychological stability and reducing stress, which can otherwise exacerbate inflammation and its neuropsychiatric effects. The combination of low TNF- α levels and employment likely represents a dual protective mechanism, where lower neuroinflammation dovetails with the psychosocial benefits of employment to substantially reduce the risk of SB. Thus, employed individuals with lower TNF- α levels experience an additive or even synergistic effect, leading to the lowest observed rates of SB. This interpretation suggests that interventions aimed at reducing inflammation while enhancing employment and social support could be particularly effective in mitigating suicide risk in populations vulnerable to depressive disorders.

Meanwhile, TNF- α levels could not significantly differentiate SB incidence among unemployed participants group. These can be understood through a psychosocial perspective. Unemployment frequently correlates with profound psychological stress, social isolation, and economic hardship, factors independently elevate the risk of depressive symptoms and SBs. The chronic stress associated with unemployment may induce a state of heightened baseline inflammation or psychological vulnerability, which could overshadow any specific effects that fluctuations in TNF- α levels might have.³⁰ Additionally, the lack of structure and social support that often ac-

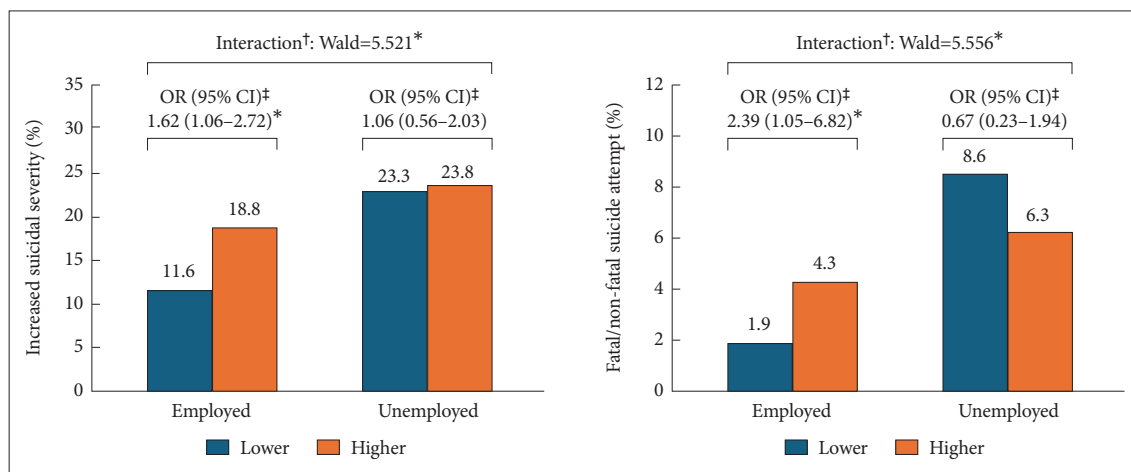


Figure 2. Dual interactive effects of sTNF- α levels and employment status with SB during 1-year follow-up (N=884). * $p < 0.05$; †interactive effects of sTNF- α levels and employment status on SB were estimated using multinomial logistic regression; *ORs (95% CI) were calculated using binary logistic regression for lower (< 0.593 pg/mL) vs. higher (≥ 0.593 pg/mL) sTNF- α levels on SB, after adjustment for age, sex, marital status, living alone, duration of present episode, number of physical disorders, current smoking, Hospital Anxiety & Depression Scale-depression subscale scores, and treatment step. sTNF- α , serum tumor necrosis factor- α ; OR, odds ratio; CI, confidence interval; SB, suicidal behavior.

companies unemployment could exacerbate mental health challenges, making individuals more susceptible to depressive symptoms and suicidal ideation regardless of their biological inflammation status.²⁹ This suggests that the psychosocial stressors linked with unemployment are sufficiently intense to maintain a high baseline risk for SB, thereby muting the potential modulating effect of TNF- α levels. Moreover, unemployed individuals may experience a phenomenon known as “allostatic load,” which refers to the cumulative burden of chronic stress and can affect various physiological systems.³¹ This condition can lead to a kind of “ceiling effect” where the added impact of biological markers like TNF- α on SB becomes negligible because the psychosocial determinants are already exerting maximal influence on the individual’s mental health.

Several important issues should be considered before drawing a conclusion. The potential for reverse causality between employment status and SB underscores the complexity of interpreting the associations observed in this study. While it may be hypothesized that employment status influences SB through various psychosocial mechanisms, such as enhanced social support and financial stability, it is equally plausible that individuals experiencing severe suicidal ideation or behavior may find it difficult to obtain or retain employment. This reciprocal relationship suggests that the causal pathways might not be straightforward and could involve multiple interacting factors. Therefore, future research should aim to use longitudinal designs with multiple time points to disentangle these potential bidirectional influences, ensuring a more robust understanding of the dynamics at play. Additionally, the issue of multiple comparisons arises from the numerous logistic re-

gression models applied to analyze a variety of variables within our study. We chose not to apply corrections for multiple comparisons, based on the focused nature of our hypothesis testing and our methodological approach. We maintained stringent significance levels and limited the number of hypothesis tests based on our preliminary analyses, which helped mitigate the risk of Type I errors that are often a concern with multiple comparisons. Each regression model and hypothesis test was specifically designed to explore distinct and substantive questions, reducing the probability of generating spurious findings from extensive data exploration.

This investigation acknowledges a few key limitations that warrant consideration. Importantly, sTNF- α levels were measured only at the baseline, which restricts our ability to assess how these levels might change in response to treatment or alterations in lifestyle habits over the study period.³² Consequently, this limitation prevents the exploration of potential correlations between dynamic changes in sTNF- α levels and SB over time. Furthermore, the classification of employment status in this study was dichotomous, categorizing individuals as either “employed” or “unemployed.” This approach does not account for the diverse types of employment—such as full-time, part-time, or self-employed—that might differently influence mental health outcomes. The absence of a more granular distinction between various employment conditions may limit our understanding of the subtle effects these factors have on SB in individuals with depressive disorders. Future studies should consider a more detailed exploration of employment types to more accurately assess their impact on mental health. Additionally, the naturalistic approach of the study meant that treatment regimens were tailored based on individual patient pref-

erences and physician guidance, not a standardized protocol. This could introduce variability in treatment effects across different physicians. However, the blinding of physicians to the sTNF- α levels minimizes the likelihood that this variability influenced the primary associations of interest. Another consideration is the significant attrition observed over the 1-year treatment phase. The attrition was predominantly among participants with poorer prognostic features, such as unemployed status or melancholic features, potentially leading to an underestimation rather than an overstatement of the associations.

Among the strengths of this study is its pioneering use of a prospective design to assess SB, an approach not commonly adopted in similar research. The robust sample size enhances the reliability of the findings, supported further by the systematic application of a structured research protocol and the use of validated and widely recognized assessment scales. Additionally, the analysis considered a comprehensive range of covariates that might influence the outcomes, ensuring a thorough exploration of the factors at play in the relationships studied.

In conclusion, our findings suggest that the interactive associations between biological markers such as sTNF- α levels and socio-economic factors like employment status significantly influence SB in patients with depressive disorders. This underscores the importance of a holistic approach in public health strategies that not only addresses biological predispositions but also integrates socio-economic interventions. Public health initiatives could therefore benefit from incorporating employment support services alongside traditional mental health interventions to reduce the risk of SB among individuals with depression. From a clinical perspective, considering sTNF- α levels in conjunction with employment status enhances the predictive accuracy for SB, providing a more balanced approach to risk assessment and management in depressive disorders. Clinicians should consider these factors together when designing personalized treatment plans. This approach might help identify patients at higher risk more effectively, allowing for interventions that are tailored not only to the clinical presentation but also to the socio-economic context of the patient, potentially improving treatment outcomes. Regarding future Research, the interaction between sTNF- α levels and employment status in predicting SB presents a compelling area for further investigation. Further studies are needed to replicate these findings in diverse clinical settings and among populations at high risk of depressive disorders to validate and expand upon our results. Additionally, longitudinal studies exploring how changes in TNF- α levels and employment status over time affect SB could provide deeper insights into the dynamic nature of these relationships, offering opportunities for timely and targeted interventions.

Supplementary Materials

The Supplement is available with this article at <https://doi.org/10.30773/pi.2025.0044>.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Jae-Min Kim, a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Jae-Min Kim. Data curation: Jae-Min Kim, Hee-Ju Kang, Ju-Wan Kim. Formal analysis: Ha-Yeon Kim, Jae-Min Kim, Ju-Yeon Lee. Funding acquisition: Jae-Min Kim, Min-Gon Kim. Investigation: Byung Jo Chun, Sung-Wan Kim, Hee-Ju Kang. Methodology: Jae-Min Kim, Sung-Wan Kim, Il-Seon Shin. Project administration: Ha-Yeon Kim, Hee-Ju Kang. Supervision: Jae-Min Kim. Validation: Jae-Min Kim, Sung-Wan Kim. Writing—original draft: Ha-Yeon Kim, Jae-Min Kim. Writing—review & editing: Ha-Yeon Kim, Jae-Min Kim.

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Funding Statement

This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. RS-2024-00440371) and CNUH-GIST research Collaboration grant (BCRI24088) funded by the Chonnam National University Hospital Biomedical Research Institute to Jae-Min Kim.

Acknowledgments

None

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